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Possibilities in bioelectronics: Super humans or science fiction?

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ABSTRACT

Recent years have led to a rapid increase in the development of neurotechnologies for diagnosis, monitoring, and treatment of conditions with neurological targets. The central driving force has been the need for next-generation devices to treat neural injury and disease, where current pharmaceutical or conventional bioelectronics have been unable to impart sufficient therapeutic effects. The advent of new therapies and advanced technologies has resulted in a reemergence of the concept of superhuman performance. This is a hypothetical possibility that is enabled when bionics are used to augment the neural system and has included the notions of improved cognitive ability and enhancement of hearing and seeing beyond the limitations of a healthy human. It is quite conceivable that a bionic eye could be used for night vision; however, the damage to both the neural system and surrounding tissues in placing such a device is only considered acceptable in the case of a patient that can obtain improvement in quality of life. There are also critical limitations that have hindered clinical translation of high-resolution neural interfaces, despite significant advances in biomaterial and bioelectronics technologies, including the advent of biohybrid devices. Surgical damage and foreign body reactions to such devices can be reduced but not eliminated, and these engineering solutions to reduce inflammation present additional challenges to the long-term performance and medical regulation. As a result, while bioelectronics has seen concepts from science fiction realized, there remains a significant gap to their use as enhancements beyond medical therapies.

I. THE EMERGENCE OF BIOELECTRONIC TECHNOLOGIES

Bioelectronics is a field that has seen rapid expansion across the recent decade as researchers and industry have explored interfacing devices with electroactive cells of the body to elicit novel insights and deliver new therapies (Solazzo *et al.*, 2019; Vitale and Litt, 2018), leading to the evolution of a bionic man (Fig. 1). While traditional bioelectronic technologies, such as pacemakers, cochlear implants, electroencephalograms (EEGs), and electromyograms (EMG), have been in the clinic for over 50 years, the development of neuropsychiatric treatments, electroceuticals, and closed loop systems has only reached the clinic within the recent decade (Portillo-Lara *et al.*, 2021). These advances have been driven by major funding across the globe including government initiatives, such as the EU Human Brain Project, the US BRAIN initiative, and the NIH SPARC initiative, and new commercial initiatives, such as Neurolink and Galvani Bioelectronics (Mathieson *et al.*, 2021; Royal Society, 2019). This has led to approved, medically regulated bioelectronic therapies for the treatment of a range of conditions spanning epilepsy, depression, immune conditions, tremor disorders, blindness, and spinal cord injury. However, it has also been postulated that these technologies could be harnessed to achieve extra-ordinary abilities such as improved cognition, night vision, and other enhanced perception when placed in healthy humans ("Elon Musk's Neuralink Is Neuroscience Theater|MIT Technology Review," 2021). While the lines between science fiction and medical therapies have blurred substantially over the recent decades (Portillo-Lara *et al.*, 2021), there is still a wide gap between state-of-the-art neurotechnology and the complexity, organization, and filtering processes of the human nervous system and, in particular, the brain (Maoz, 2021).

To contextualize the current bioelectronic technologies, the leading bionic eye devices can improve the mobility of a blind patient without the use of visual aids; however, patients with these devices remain legally blind (Finn *et al.*, 2018). Despite this, it is feasible that bionic eyes could be used to enable night vision, as these devices use external cameras to detect the environment (Sarosh *et al.*, 2019; Lovell *et al.*, 2007). In hearing, where cochlear implants have been in use for over 40 years, the spectrum of sounds detected through 3500 inner hair cells in the normally hearing human ear is more simplistically represented by 22 electrodes in an augmenting implant (Dalrymple *et al.*, 2020;

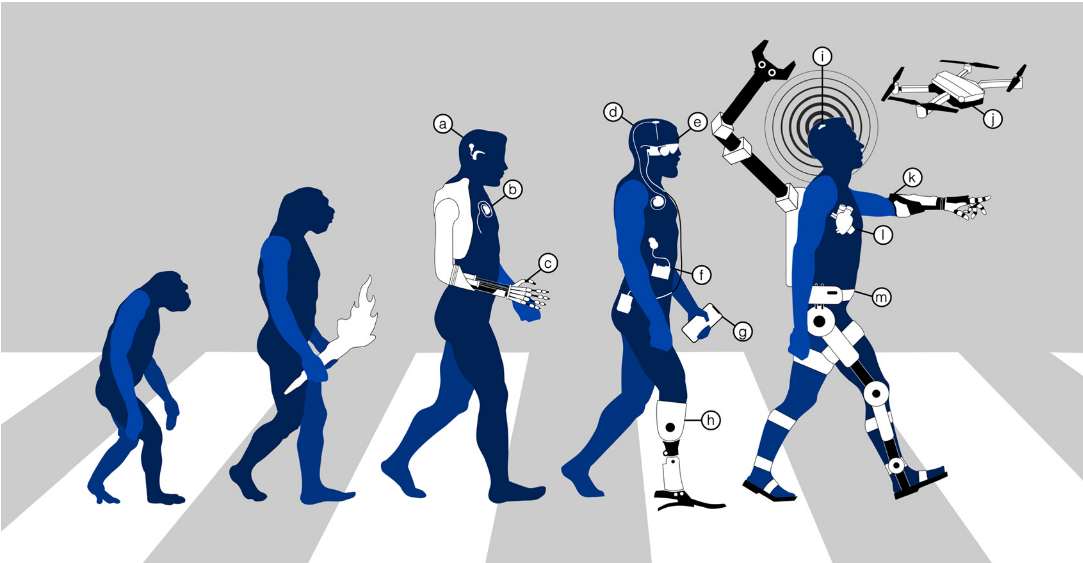

FIG. 1. The evolution of the bioelectronic superhuman. From the first generation of bionics: (a) cochlear implant, (b) cardiac pacemaker, and (c) static prosthetics to the current day state-of-the-art bionics: (d) bionic eye, (e) deep brain stimulator, and (f) bionic pancreas with (g) smartphone app control and (h) powered limb prostheses. The next-generation superhuman bionics are predicted to include (i) brain computer interfaces for control of (j) unmanned vehicles and other external devices, (k) bionic arm with sensory feedback, (l) total bionic heart replacement, and (m) exoskeletons for augmenting strength and stamina.

Joung, 2013). This has been found to be sufficient for helping deaf children learn to vocally communicate but presents major limitations for sound sourcing in a crowded room and ability to perceive complex sounds such as music. Ideally, an augmenting device for replacing or correcting functions of the nervous system would enable connections between devices and individual cells (Goding *et al.*, 2017; Grill *et al.*, 2009). This resolution of communication would theoretically enable devices to replicate healthy human neural functions and potentially reach levels of optimization that could be considered superhuman. However, fundamental challenges in engineering have prevented the development of such high-resolution technologies. Primarily, these challenges have included the ability to safely reduce the size of electrodes, the inflammatory and foreign body response caused by synthetic and, in particular, high stiffness device materials, and the capability to miniaturize electronics and retain high fidelity data transfer to external computers (Mehdi *et al.*, 2015).

II. BIOHYBRID APPROACHES FOR SUPER-RESOLUTION

Rapid development of nano and microscale electronics has led to impressive scalability in hardware and data transfer, mitigating the limitations in signal processing. However, the interface with the human body and, in particular, the electrodes has experienced significant hurdles to clinical applications, despite a wide variety of innovations. To obtain high specificity of neural control, it is necessary to be close to the target cells, making implantable devices preferable over noninvasive wearable devices. In an attempt to improve device communication and mediate the foreign body response at the implant site, the development of soft, organic based electronics and biohybrid technologies incorporating biomolecules and even cells have been proposed (Aregueta-Robles *et al.*, 2014; Portillo-Lara *et al.*, 2021; Kamm *et al.*, 2018). Flexible electronics based on conductive polymers (Novikov *et al.*, 2020; Cuttaz *et al.*, 2021) or carbon conductors (Bareket-Keren and Hanein, 2013; Varnava, 2020) embedded within hydrogels and elastomers have provided an alternative to stiff metallic implantable electrodes. These approaches reduce the long-term foreign body response that results in insulative scar tissue isolating electronic devices but do not remove the risk and tissue damage associated with surgical implantation. The design of highly miniaturized probe electrodes has shown significant promise in reducing implantation damage while remaining imperceptible to local immune cells (Varnava, 2020); however, retaining a robust electrical connection to hardware and safely delivering stimulation to tissues through such a small interface remains an engineering challenge. An alternative approach that aims to reduce device invasiveness is the use of remotely addressable systems (Xu *et al.*, 2020), where magnetic or thermal stimulation of injected nanomaterials enables activation of the nervous tissue (Chen *et al.*, 2015; Portillo-Lara *et al.*, 2021). The latter innovation has significant potential for reducing surgically induced damage but presents new challenges to accurate placement of nanomaterials and the ability to continue it to stimulate or record from an area of the nervous system as cells undergo renewal and remodeling, displacing the mediating nanomaterial target.

In *APL Bioengineering*, biohybrid technologies have presented advances within the fields of tissue engineering (Kaufman *et al.*, 2020; Ehsanipour *et al.*, 2021), neurophysiology (Maoz, 2021), and *in vitro* culture models (Kamm *et al.*, 2018). The integration of electronics within culture systems to enable organ and lab-on-chip has demonstrated how recordings from complex tissues can be enabled by combining the principles of tissue engineering with bioelectronics (Visone *et al.*, 2018; Maoz, 2021). Learning from these tissue engineering approaches, such as those detailed in

Oksdath *et al.* (2018) and Ehsanipour *et al.* (2021), has been critical to the development of implantable bioelectronics that are more readily integrated into the soft, electroexcitable tissues. Maclean *et al.* (2018) reviewed biomaterials for traumatic brain injury, outlining the design criteria for an ideal material that promotes integration of cortical neurons. The adoption of these criteria for interfacing brain electronics has led to the development of living bioelectronics (Goding *et al.*, 2017; Vallejo-Giraldo *et al.*, 2021), where cells encapsulated at the surface of bionic devices can promote synaptic connections to the endogenous nervous system. These biohybrid technologies present the first steps toward cell level connections that could facilitate super-resolution connections between devices and the human body.

While these advances in electronics combined with biomaterials and tissue engineering do not preclude the development of super-resolution implantable bioelectronics, there is still critical understanding of neural system development, repair, and remodeling (Maoz, 2021) that must be gained to enable safe and effective placement of enhancing technologies. This knowledge gap largely precludes the use of these devices as augmenting technologies beyond the natural capacity of the non-impaired neural system (Portillo-Lara *et al.*, 2021). Implantable devices are known to impart substantial injury during the surgical placement (Menciassi and Iacovacci, 2020) and while engineering approaches can reduce injury, there remains a significant gap in understanding the impact of intervention on brain plasticity and rewiring (Mateos-Aparicio and Rodríguez-Moreno, 2019). It is known that over time, neural networks will undergo changes according to the inputs, including electrical, magnetic, or optoelectronic stimulation (Huang *et al.*, 2020; Crawford and San-Miguel, 2020). This has been to the benefit of patients impacted by disorders of the neural system, such that cells that have not been degraded by disease or injury can be recruited to help replace a lost functionality. Intervention within a fully functional, healthy neural system will cause damage that could lead to loss of natural function following surgery; however, changes in the neural network as a result of the implant stimulation could impart a range of side effects, the impact of which is entirely unchartered (Drew, 2019). It is feasible to consider that in an attempt to impart improved cognition, damage or reprogramming within the cortex could result in significant changes to a subjects neuropsychiatric state or logical reasoning. The risk of these unknowns highlights the need for extreme caution in suggesting that bioelectronics could be used to realize superhuman.

III. SUPERHUMAN THERAPEUTICS NOT SUPERPOWERS

It is clear that neurotechnologies and, in particular, implantable technologies have undergone rapid advances across the recent decade, enabling a range of new therapeutic interventions. In particular, the merging of approaches learned from tissue engineering, biomaterials, and bionics has facilitated the emergence of the field of organic and living bioelectronics that has the capacity to enable higher resolution technologies. These new methods of intervention coupled with developments in computational methods and microelectronics will continue to blur the lines between science fiction and healthcare; however, super-resolution devices and augmentation to produce performance beyond the functioning healthy nervous system remain a futuristic hypothetical.

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REFERENCES

Aregueta-Robles, U. A., Woolley, A. J., Poole-Warren, L. A., Lovell, N. H., and Green, R. A., "Organic electrode coatings for next-generation neural interfaces," Front. Neuroeng. **7**, 15 (2014).

Bareket-Keren, L., and Hanein, Y., "Carbon nanotube-based multi electrode arrays for neuronal interfacing: Progress and prospects," Front. Neural Circuits **6**, 122 (2013).

Chen, R., Romero, G., Christiansen, M. G., Mohr, A., and Anikeeva, P., "Wireless magnetothermal deep brain stimulation," Science **347**(6229), 1477–1480 (2015).

Crawford, Z., and San-Miguel, A., "An inexpensive programmable optogenetic platform for controlled neuronal activation regimens in *C. elegans*," APL Bioeng. **4**(1), 016101 (2020).

Cuttaz, E. A., Chapman, C. A. R., Syed, O., Goding, J. A., and Green, R. A., "Stretchable, fully polymeric electrode arrays for peripheral nerve stimulation," Adv. Sci. **8**, 2004033 (2021).

Dalrymple, A. N., Robles, U. A., Huynh, M., Nayagam, B. A., Green, R. A., Poole-Warren, L. A., Fallon, J. B., and Shepherd, R. K., "Electrochemical and biological performance of chronically stimulated conductive hydrogel electrodes," J. Neural Eng. **17**(2), 026018 (2020).

Drew, L., "The ethics of brain–computer interfaces," Nature **571**(7766), S19–S21 (2019).

Ehsanipour, A., Sathialingam, M., Rad, L. M., de Rutte, J., Bierman, R. D., Liang, J., Xiao, W., di Carlo, D., and Seidlits, S. K., "Injectable, macroporous scaffolds for delivery of therapeutic genes to the injured spinal cord," APL Bioeng. **5**(1), 016104 (2021).

Emerging Technologies Working Group, *IHuman Blurring Lines Between Mind and Machine* (The Royal Society, 2019), available at https://royalsociety.org/-/media/policy/projects/ihuman/report-neural-interfaces.pdf.

See https://www.technologyreview.com/2020/08/30/1007786/elon-musks-neuralink-demo-update-neuroscience-theater/ for "Elon Musk's Neuralink Is Neuroscience Theater|MIT Technology Review"; accessed 19 November 2021.

Finn, A. P., Grewal, D. S., and Vajzovic, L., "Argus II retinal prosthesis system: A review of patient selection criteria, surgical considerations, and post-operative outcomes," Clin. Ophthalmol. **12**, 1089 (2018).

Goding, J. A., Gilmour, A. D., Aregueta-Robles, U. A., Hasan, E. A., and Green, R. A., "Living bioelectronics: Strategies for developing an effective long-term implant with functional neural connections," Adv. Funct. Mater. **28**, 1702969 (2017).

Goding, J., Gilmour, A., Robles, U. A., Poole-Warren, L., Lovell, N., Martens, P., and Green, R., "A living electrode construct for incorporation of cells into bionic devices," MRS Commun. **7**, 487–495 (2017).

Grill, W. M., Norman, S. E., and Bellamkonda, R. V., "Implanted neural interfaces: Biochallenges and engineered solutions," Annu. Rev. Biomed. Eng. **11**(1), 1–24 (2009).

Huang, N. F., Chaudhuri, O., Cahan, P., Wang, A., Engler, A. J., Wang, Y., Kumar, S., Khademhosseini, A., and Li, S., "Multi-scale cellular engineering: From molecules to organ-on-a-chip," APL Bioeng. **4**(1), 010906 (2020).

Mehdi, J., Skousen John, L., Weder, C., and Capadona Jeffrey, R., "Progress towards biocompatible intracortical microelectrodes for neural interfacing applications," J. Neural Eng. **12**(1), 11001 (2015).

Joung, Y.-H., "Development of implantable medical devices: From an engineering perspective," Int. Neurourol. J. **17**(3), 98–106 (2013).

Kamm, R. D., Bashir, R., Arora, N., Dar, R. D., Gillette, M. U., Griffith, L. G., Kemp, M. L. *et al.*, "Perspective: The promise of multi-cellular engineered living systems," APL Bioeng. **2**(4), 040901 (2018).

Kaufman, C. D., Liu, S. C., Cvetkovic, C., Lee, C. A., Naseri Kouzehgarani, G., Gillette, R., Bashir, R., and Gillette, M. U., "Emergence of functional

neuromuscular junctions in an engineered, multicellular spinal cord-muscle bioactuator," APL Bioeng. **4**(2), 026104 (2020).
Lovell, N. H., Hallum, L. E., Chen, S. C., Dokos, S., Byrnes-Preston, P., Green, R., Poole-Warren, L., Lehmann, T., and Suaning, G. J., "Advances in retinal neuroprosthetics," in *Handbook of Neural Engineering*, edited by M. Akay (John Wiley & Sons, Inc., Hoboken, NJ, 2007), pp. 337–356.
Maclean, F. L., Horne, M. K., Williams, R. J., and Nisbet, D. R., "Review: Biomaterial systems to resolve brain inflammation after traumatic injury," APL Bioeng. **2**(2), 021502 (2018).
Maoz, B. M., "Brain-on-a-chip: Characterizing the next generation of advanced in vitro platforms for modeling the central nervous system," APL Bioeng. **5**(3), 030902 (2021).
Mateos-Aparicio, P., and Rodríguez-Moreno, A., "The impact of studying brain plasticity," Front. Cell. Neurosci. **13**, 66 (2019).
Mathieson, K., Denison, T., and Winkworth-Smith, C., *A Transformative Roadmap for Neurotechnology in the UK* (KTN, 2021), available at https://ktn-uk.org/wp-content/uploads/2021/06/A-transformative-roadmap-for-neurotechnology-in-the-UK.pdf.
Menciassi, A., and Iacovacci, V., "Implantable biorobotic organs," APL Bioeng. **4**(4), 040402 (2020).
Novikov, A., Goding, J., Chapman, C., Cuttaz, E., and Green, R. A., "Stretchable bioelectronics: Mitigating the challenges of the percolation threshold in conductive elastomers," APL Mater. **8**(10), 101105 (2020).
Oksdath, M., Perrin, S. L., Bardy, C., Hilder, E. F., Deforest, C. A., Arrua, R. D., and Gomez, G. A., "Review: Synthetic scaffolds to control the biochemical, mechanical, and geometrical environment of stem cell-derived brain organoids," APL Bioeng. **2**(4), 041501 (2018).
Portillo-Lara, R., Goding, J. A., and Green, R. A., "Adaptive biomimicry: Design of neural interfaces with enhanced biointegration," Curr. Opin. Biotechnol. **72**, 62–68 (2021).
Portillo-Lara, R., Tahirbegi, B., Chapman, C. A. R., Goding, J. A., and Green, R. A., "Mind the gap: State-of-the-art technologies and applications for EEG-based brain–computer interfaces," APL Bioeng. **5**(3), 031507 (2021).
Sarosh, P., Parah, S. A., and Sarosh, R., "Role of multimedia in medicine: Study of visual prosthesis," in *Handbook of Multimedia Information Security: Techniques and Applications* (Springer International Publishing, 2019), pp. 559–576.
Solazzo, M., O'Brien, F. J., Nicolosi, V., and Monaghan, M. G., "The rationale and emergence of electroconductive biomaterial scaffolds in cardiac tissue engineering," APL Bioeng. **3**(4), 041501 (2019).
Vallejo-Giraldo, C., Genta, M., Goding, J., and Green, R., "Biomimetic approaches towards device-tissue integration," in *Handbook of Neuroengineering* (Springer International Publishing, 2021), pp. 1–26.
Varnava, C., "Connecting to the brain with bundled microwires," Nat. Electron. **3**(4), 186–186 (2020).
Visone, R., Talò, G., Occhetta, P., Cruz-Moreira, D., Lopa, S., Pappalardo, O. A., Redaelli, A., Moretti, M., and Rasponi, M., "A microscale biomimetic platform for generation and electro-mechanical stimulation of 3D cardiac microtissues," APL Bioeng. **2**(4), 046102 (2018).
Vitale, F., and Litt, B., "Bioelectronics: The promise of leveraging the body's circuitry to treat disease," Bioelectron. Med. **1**(1), 3–7 (2018).
Xu, Z., Xu, J., Yang, W., Lin, H., and Ruan, G., "Remote neurostimulation with physical fields at cellular level enabled by nanomaterials: Toward medical applications," APL Bioeng. **4**(4), 040901 (2020).